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Clinical Study

# Rapid eye movement sleep behavior disorder after bilateral subthalamic stimulation in Parkinson's disease

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ABSTRACT

The effect of subthalamic nucleus (STN) deep brain stimulation (DBS) on rapid eye movement sleep behavior disorder (RBD) in Parkinson's disease (PD) is not well known. We evaluated the change in the incidence of probable RBD after bilateral STN DBS in PD patients. Ninety patients with PD treated with bilateral STN DBS underwent retrospective assessment of RBD by interview before and after DBS. Forty-seven (52.2%) of the 90 patients had RBD preoperatively. RBD was resolved only in one patient and persisted in 46 patients at 1 year after DBS. RBD developed *de novo* in 16 patients (*de novo* RBD group) within 1 year after DBS, resulting in 62 (68.9%) of the 90 patients having RBD 1 year after DBS. Patients with RBD at any time within 1 year after DBS (RBD group, n = 63) were older than the patients without RBD (non-RBD group, n = 27). The sum of the Unified Parkinson Disease Rating Scale (UPDRS) axial score for the "on" state was lower in the RBD group than in the non-RBD group after DBS ($p = 0.029$). Comparing the *de novo* RBD group and non-RBD group, the UPDRS Part III and total score and the levodopa equivalent daily doses for the "on" states decreased more in the *de novo* RBD group than in the non-RBD group ($p < 0.05$). The incidence of clinical RBD increased after bilateral STN DBS because *de novo* RBD developed and pre-existing RBD persisted after DBS.



## 1. Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is clinically defined as recurrent dream enactment behavior and REM sleep without atonia (RSWA) by polysomnography [1]. RBD is found in up to 60% of patients with Parkinson's disease (PD) [2]. Prospective studies suggest that RBD is a potential preclinical marker of neurodegenerative disease, which will eventually develop into synucleinopathies in at least 40–65% of patients [3].

Although RBD is a valuable preclinical marker, the pathophysiology of RBD is not fully understood. Current understanding suggests that the pontine and medullary areas could be responsible for the loss of muscle atonia during REM sleep with concurrent dream enactment [4].

Subthalamic nucleus (STN) deep brain stimulation (DBS) improves non-motor symptoms as well as motor symptoms of PD [5]. Considering the anatomical location of the STN and the pathophysiology of RBD, STN DBS will theoretically not affect the prevalence or progress of RBD. Several previous studies showed that RBD is not affected by STN DBS, even though STN DBS improves subjective and objective sleep measures, including sleep efficiency and nocturnal mobility [6–9]. From another aspect, Nishida et al. reported more recently that normal atonic REM sleep time increased postsurgically [10]. However, the sample numbers used in these previous studies were very small (10 or 11 patients), although they did use appropriate methodology, such as polysomnography [6–9].

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Therefore, it will be valuable to assess the change in RBD after STN DBS compared to the preoperative state in a large population, even with a retrospective survey.

## 2. Methods

### 2.1. Patients

We performed bilateral STN DBS in 124 patients with PD from March 2005 to March 2010 at the Movement Disorder Center at Seoul National University Hospital (SNUH). Among them, six patients had staged bilateral surgery, 10 patients had repositioning, nine patients died (unrelated to the DBS surgery), and nine patients were lost to follow-up. A total of 90 patients were enrolled (40 men and 50 women). Two of the 90 patients had the Parkin mutation and were enrolled because there was a report that RBD is more frequent in patients with the PARK2 mutation, even though it is not a synucleinopathy [11]. This study was carried out after thoroughly explaining it to the potential subjects and receiving their consent. This study was approved by the Institutional Review Board at SNUH.

### 2.2. Clinical assessment

A search for patients with RBD was conducted from May 2010 to March 2011 using the Seoul National University Hospital database. We interviewed all the caregivers and patients regarding the presence of RBD before and after DBS as well as when the RBD developed, retrospectively. Additionally, we reviewed the medical records. A positive diagnosis of clinical RBD was obtained by the clinicians Y.E.K. and H.J.Y. conducting interviews according to the minimal diagnostic criteria for parasomnias provided in the International Classification of Sleep Disorders-Revised (ICSD-R) [12]. The diagnostic criteria for RBD included limb or body movement associated with dream mentation and at least one of the following: harmful or potentially harmful sleep behavior, dreams appear to be "acted out", or sleep behaviors disrupt sleep continuity. Additionally, the onset of RBD was divided into before surgery, within 1 year postoperatively and after 1 year postoperatively. We used other clinical variables for the analysis, including demographic features, Unified Parkinson Disease Rating Scale (UPDRS), Hoehn and Yahr stage and levodopa equivalent daily dose (LEDD), Beck Depression Inventory, and the Mini Mental Status Examination which have been evaluated and are routine practice during the preoperative state and 1 year after DBS prospectively [13]. All drugs that could affect the severity of RBD were reviewed from the medical records [2]. The UPDRS axial score includes speech, neck rigidity, arising from a chair, posture, gait, postural instability, and body bradykinesia.

### 2.3. Statistical assessment

McNemar's test was used to compare the prevalence of RBD before and after DBS. Independent sample *t*-test was used for the analysis of continuous variables between two independent groups. The change in clinical valuables before and after DBS was tested by paired *t*-test. A *p* value of <0.05 was considered significant. These statistical analyses were conducted using the Statistical Package for the Social Sciences version 19.0 (SPSS, Chicago, IL, USA).

## 3. Results

A total of 90 patients were enrolled in this study and Table 1 presents the demographic features of all the subjects.

**Table 1**
Demographic features of all subjects undergoing bilateral subthalamic stimulation for Parkinson's disease

| N = 90 | Preop | Postop (1 year) | *p* value[a] |
|---|---|---|---|
| Sex (M:F) | 40:50 | | |
| Current age, years | 62.98 ± 7.87 (34–78) | | |
| PD duration, years | 14.84 ± 4.52 (7–31) | | |
| H&Y stage | 2.25 ± .57 | 2.26 ± .62 | 0.881 |
| LEDD | 1032.58 ± 590.61 | 369.54 ± 409.67 | 0.000 |
| MMSE | 27.24 ± 2.30 | 26.75 ± 2.61 | 0.089 |
| BDI | 18.74 ± 10.33 | 19.44 ± 10.45 | 0.594 |
| UPDRS total score "on" | 29.32 ± 14.24 | 24.99 ± 12.60 | 0.050 |

Values are expressed as the mean ± standard deviation. Ranges are in parentheses where relevant.
[a] Paired *t*-test.
BDI = Beck Depression Inventory, F = female, H&Y = Hoehn and Yahr stage, LEDD = levodopa equivalent daily dose, M = male, MMSE = Mini Mental Status Examination, PD = Parkinson's disease, Postop = postoperatively, Preop = preoperatively, UPDRS total score "on" = Unified Parkinson Disease Rating Scale total score for the medication "on" state.

Forty-seven (52.2%) of the 90 patients had RBD preoperatively. At 1 year after DBS, the prevalence of RBD increased with 62 (68.9%) patients out of 90 having RBD, a statistically significant increase compared to the preoperative state ($p < 0.001$). At the time of the interviews (mean interval until interview after surgery 56.02 ± standard deviation 19.10 months), 69 patients (76.6%) had clinical RBD because RBD developed in an additional seven patients later than 1 year after DBS.

*De novo* RBD developed in 16 patients within 1 year after DBS and continued up to the time of the interviews (May 2010 to March 2011). Among these 16 patients, RBD developed immediately after surgery in four patients. Among the 47 patients with preoperative RBD, 46 patients still had RBD postoperatively while RBD disappeared in the one remaining patient after DBS. Among the 46 patients who still had RBD after DBS, the severity of symptoms decreased in 13 patients after DBS (Fig. 1). Among the 16 patients with *de novo* RBD, a change in drug, which can alter the frequency or severity of RBD after DBS, occurred in four patients. Tricyclic antidepressants were newly prescribed to two patients after surgery, and amitriptyline and triazolam were stopped in one patient and both started in another patient after surgery (Supp. Table 1). In the two patients who had the PARK2 mutation, RBD was not observed over the entire period in one patient and developed within 1 year after DBS in the other patient.

When comparing patients with RBD at any point within 1 year after DBS (RBD group, n = 63) and patients who never had RBD at 1 year after DBS (non-RBD group, n = 27), the RBD group was older than the non-RBD group ($p = 0.042$). The UPDRS axial scores for the DBS "on" and medication "on" states decreased more in the RBD group than in the non-RBD group ($p = 0.029$) (Table 2).

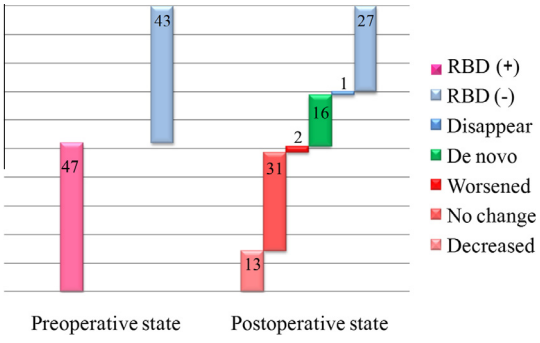


**Fig. 1.** Comparative change in rapid eye movement sleep behavior disorder (RBD) after subthalamic nucleus deep brain stimulation.

**Table 2**
Comparison of clinical characteristics between patients undergoing bilateral subthalamic stimulation for Parkinson's disease with and without rapid eye movement sleep behavior disorder over the study period

| Variables | | Non-RBD group | RBD group | *p* value[a] |
|---|---|---|---|---|
| Patients (M/F) | | 27(11/16) | 63(29/34) | |
| Age, years | | 60.41 ± 8.91 | 64.08 ± 7.17 | **0.042** |
| Sx Duration, years | | 13.85 ± 3.91 | 15.27 ± 4.72 | 0.174 |
| Preoperative state | UPDRS part III MxOn | 17.04 ± 9.60 | 190.97 ± 120.53 | 0.281 |
| | UPDRS part III MxOff | 39.22 ± 13.96 | 410.94 ± 140.65 | 0.415 |
| | UPDRS total MxOn | 25.70 ± 11.60 | 310.38 ± 160.72 | 0.112 |
| | UPDRS total MxOff | 50.22 ± 16.32 | 550.44 ± 170.45 | 0.188 |
| | UPDRS Axial 7 MxOn | 4.53 ± 1.88 | 50.84 ± 30.37 | 0.063 |
| | UPDRS Axial 7 MxOff | 10.87 ± 4.42 | 120.09 ± 40.89 | 0.269 |
| | LEDD | 878.84 ± 477.40 | 10950.33 ± 6130.38 | 0.106 |
| | MMSE | 27.85 ± 2.33 | 260.97 ± 20.16 | 0.094 |
| | BDI | 17.12 ± 8.26 | 200.07 ± 100.99 | 0.224 |
| At 1 year after DBS | UPDRS part III DBSOn MxOn | 15.67 ± 7.00 | 140.66 ± 70.87 | 0.586 |
| | UPDRS part III DBSOn MxOff | 19.31 ± 9.27 | 190.00 ± 90.30 | 0.890 |
| | UPDRS total DBSOn MxOn | 24.00 ± 10.24 | 250.40 ± 130.53 | 0.695 |
| | UPDRS total DBSOn MxOff | 32.18 ± 13.60 | 330.10 ± 140.42 | 0.804 |
| | UPDRS Axial 7 DBSOn MxOn | 6.05 ± 4.71 | 40.84 ± 20.70 | 0.202 |
| | UPDRS Axial 7 DBSOn MxOff | 6.74 ± 4.69 | 60.47 ± 30.09 | 0.752 |
| | LEDD | 293.81 ± 331.66 | 4010.83 ± 4370.24 | 0.263 |
| | MMSE | 26.76 ± 3.52 | 260.45 ± 20.68 | 0.660 |
| | BDI | 17.04 ± 9.90 | 200.83 ± 100.73 | 0.128 |
| Change of values | UPDRS part III DBSOn MxOn | −2.13 ± 9.80 | −50.45 ± 130.53 | 0.278 |
| | UPDRS part III DBSOn MxOff | −18.21 ± 12.49 | −220.78 ± 140.42 | 0.178 |
| | UPDRS total DBSOn MxOn | −0.29 ± 11.72 | −50.74 ± 180.76 | 0.314 |
| | UPDRS total DBSOn MxOff | −15.05 ± 13.78 | −220.66 ± 180.73 | 0.103 |
| | UPDRS Axial 7 DBSOn MxOn | 1.37 ± 4.60 | −10.19 ± 30.98 | **0.029** |
| | UPDRS Axial 7 DBSOn MxOff | −3.62 ± 5.29 | −50.73 ± 40.70 | 0.073 |
| | LEDD | −572.68 ± 355.11 | −7010.55 ± 5450.83 | 0.196 |
| | MMSE | −0.54 ± 1.93 | −00.47 ± 20.79 | 0.913 |
| | BDI | 0.16 ± 13.14 | 00.95 ± 110.12 | 0.783 |

Values are expressed as the mean ± standard deviation.
Bold indicates statistical significance.
[a] Independent *t*-test.
BDI = Beck Depression Inventory, DBS = deep brain stimulation, F = female, LEDD = levodopa equivalent daily dose, M = male, MMSE = Mini Mental Status Examination; Mx = medication, Non-RBD group = patients who never experienced rapid eye movement sleep behavior disorder for at least 1 year after deep brain stimulation, RBD group = patients with rapid eye movement sleep behavior disorder at any time within 1 year after deep brain stimulation, Sx = symptom, UPDRS = Unified Parkinson Disease Rating Scale, UPDRS Axial 7 = Unified Parkinson Disease Rating Scale for speech, neck rigidity, rising from a chair, posture, gait, postural instability, and body bradykinesia.

We compared the clinical characteristics between the non-RBD group (n = 27) and patients who had *de novo* RBD within 1 year after DBS (*de novo* RBD group, n = 16) (Table 3). The UPDRS total score for the medication "on" state was significantly higher in the *de novo* RBD group than in the non-RBD group preoperatively ($p = 0.032$). The UPDRS part III or total score for the DBS "on" and medication "off" states showed a significantly greater decline in the *de novo* RBD group than in the non-RBD group ($p = 0.024$ and 0.015, respectively). The LEDD after DBS also significantly decreased more in the *de novo* RBD group than in the non-RBD group ($p = 0.047$).

## 4. Discussion

This study showed that the incidence of clinical RBD increased after bilateral STN DBS as *de novo* RBD developed and pre-existing RBD persisted after DBS. *De novo* RBD occurred in 16 (37.2%) out of 43 patients within 1 year after DBS. The prevalence of RBD was 52.2% preoperatively, 68.9% at 1 year after surgery and 76.7% at the time of the interview (mean interval until interview after surgery 56.02 ± 19.10 months). Considering the anatomical location of STN for DBS and the pontomedullary area responding to RBD, STN DBS will theoretically not affect the incidence or progress of RBD. There are several possible explanations as to why the results of our study do not correspond to our hypothesis. Gagnon et al. reported that one half of patients with RSWA were not diagnosed by clinical history [14]. RSWA is often observed in PD, even if patients do not have clinical dream enactment behavior, and is a prodromal sign of RBD [10,15]. Furthermore, dreaming can be augmented by brain injury or drug withdrawal [16]. Considering this, we postulate that the patients in this study had only RSWA or RBD with mild clinical symptoms, which became aggravated after DBS.

Additionally some reports support that dopaminergic drugs reduce clinical RBD [17–19]. A decrease in dopaminergic drug dose after DBS and brain injury from surgery could contribute to RBD becoming clinically significant after DBS. Our finding that the LEDD significantly decreased in the *de novo* RBD group after DBS supports this theory. There are other possibilities, including that several drugs causing the suppression of RBD could have been stopped, or drugs causing the aggravation of RBD could have been started after DBS. However, there was no significant relationship between the changes in relevant drugs and the change in RBD symptoms (Supp. Table 1). The increased incidence of RBD with time can be explained by its natural course according to PD duration irrespective of STN DBS. Several papers have shown that RBD is associated with a longer duration of PD or old age [4,20–23]. However, considering the increasing rate for the incidence of RBD, RBD developed significantly within the first year after DBS compared to more than 1 year after DBS. Furthermore, RBD developed immediately in four patients after DBS.

The mechanism of RBD is still not fully understood. In this study, patients with *de novo* RBD showed greater improvement in motor symptoms and a greater decrease in LEDD than the non-RBD group, which means that patients with better anatomical positioning in the motor STN may have a greater chance of

**Table 3**
Comparison of clinical characteristics between patients undergoing bilateral subthalamic stimulation for Parkinson's disease with *de novo* rapid eye movement sleep behavior disorder and without rapid eye movement sleep behavior disorder

| Variables | | Non-RBD | De novo RBD | *p* value[a] |
|---|---|---|---|---|
| Patients (M/F) | | 27 (12/16) | 16 (8/8) | |
| Age, years | | 60.41 ± 8.91 | 64.13 ± 7.94 | 0.177 |
| Sx Duration, years | | 13.85 ± 3.91 | 15.56 ± 6.24 | 0.274 |
| Preoperative state | UPDRS part III MxOn | 17.04 ± 9.60 | 210.38 ± 140.00 | 0.235 |
| | UPDRS part III MxOff | 39.22 ± 13.96 | 440.91 ± 170.08 | 0.242 |
| | UPDRS total MxOn | 25.70 ± 11.60 | 340.63 ± 140.50 | **0.032** |
| | UPDRS total MxOff | 50.22 ± 16.32 | 590.59 ± 160.25 | 0.076 |
| | UPDRS Axial 7 MxOn | 4.54 ± 1.88 | 60.47 ± 30.58 | 0.059 |
| | UPDRS Axial 7 MxOff | 10.87 ± 4.42 | 120.56 ± 60.43 | 0.312 |
| | LEDD | 878.84 ± 477.40 | 11930.89 ± 7690.83 | 0.154 |
| | MMSE | 27.85 ± 2.32 | 260.87 ± 10.96 | 0.178 |
| | BDI | 17.12 ± 8.26 | 190.93 ± 100.26 | 0.342 |
| At 1 year after DBS | UPDRS part III DBSOn MxOn | 15.67 ± 7.00 | 130.43 ± 80.05 | 0.339 |
| | UPDRS part III DBSOn MxOff | 19.31 ± 9.27 | 160.43 ± 80.05 | 0.328 |
| | UPDRS total DBSOn MxOn | 26.20 ± 12.44 | 270.29 ± 120.43 | 0.804 |
| | UPDRS total DBSOn MxOff | 32.18 ± 13.60 | 310.29 ± 110.79 | 0.844 |
| | UPDRS Axial 7 DBSOn MxOn | 5.92 ± 4.39 | 50.77 ± 30.08 | 0.906 |
| | UPDRS Axial 7 DBSOn MxOff | 6.74 ± 4.68 | 60.73 ± 30.11 | 0.996 |
| | LEDD | 293.81 ± 331.66 | 2920.42 ± 4930.17 | 0.991 |
| | MMSE | 26.76 ± 3.52 | 260.15 ± 30.13 | 0.604 |
| | BDI | 17.04 ± 9.90 | 180.77 ± 90.64 | 0.607 |
| Change over time | UPDRS part III DBSOn MxOn | −2.13 ± 9.80 | −80.93 ± 120.05 | 0.061 |
| | UPDRS part III DBSOn MxOff | −18.21 ± 12.49 | −280.10 ± 130.09 | **0.024** |
| | UPDRS total DBSOn MxOn | 1.4 ± 13.28 | −70.8 ± 150.07 | 0.068 |
| | UPDRS total DBSOn MxOff | −15.05 ± 13.78 | −270.18 ± 130.10 | **0.015** |
| | UPDRS Axial 7 DBSOn MxOn | 1.48 ± 4.37 | −10.00 ± 30.01 | 0.060 |
| | UPDRS Axial 7 DBSOn MxOff | −3.62 ± 5.29 | −50.93 ± 50.08 | 0.182 |
| | LEDD | −572.68 ± 355.11 | −9010.47 ± 5600.15 | **0.047** |
| | MMSE | −0.54 ± 1.93 | −00.75 ± 30.02 | 0.803 |
| | BDI | 0.16 ± 13.14 | −00.33 ± 130.62 | 0.916 |

Values are expressed as the mean ± standard deviation.
Bold indicates statistical significance.
[a] Independent *t*-test.
BDI = Beck Depression Inventory, DBS = deep brain stimulation, *De novo* RBD = patients who had newly developed rapid eye movement sleep behavior disorder within 1 year after deep brain stimulation, F = female, LEDD = levodopa equivalent daily dose, M = male, MMSE = Mini Mental Status Examination; Mx = medication, Non-RBD group = patients who never experienced rapid eye movement sleep behavior disorder for at least 1 year after deep brain stimulation, RBD group = patients with rapid eye movement sleep behavior disorder at any time within 1 year after deep brain stimulation, Sx = symptoms, UPDRS = Unified Parkinson Disease Rating Scale, UPDRS Axial 7 = Unified Parkinson Disease Rating Scale for speech, neck rigidity, rising from a chair, posture, gait, postural instability, and body bradykinesia.

developing *de novo* RBD. This implies that the STN could be associated with the pathway that regulates REM sleep. Even though the role of the STN in REM sleep regulation has yet to be determined, one study suggested that STN can play a role in the ascending activating network during REM sleep. They reported that a subthalamic ponto-geniculo-occipital-like wave, which has been recorded during REM sleep in a cat, was recorded during REM sleep in humans with PD using polysomnography and DBS electrode recordings [24]. In addition, there is one case report in which RBD presented immediately after implantation for subthalamic stimulation [25]. This study suggests that some fiber tracts to the pontomedullary area, which is responsible for REM sleep with atonia, are damaged by DBS, regardless of whether the fiber tract is located in the STN or *en route* to the STN causing problems in the regulation of REM sleep [25]. This suggests that the pathological mechanism of RBD is not confined to the lower brain stem and the STN could have a role in the mechanism of RBD.

This study has the limitation of being a retrospective study; therefore, there is the possibility of recall bias. However, we carefully investigated RBD and reviewed the medical records thoroughly. In addition, we did not confirm RBD by polysomnography. Other kinds of parasomnias could be misdiagnosed as RBD. Further prospective evaluation using polysomnography is required.

In conclusion, the incidence of clinical RBD increased after bilateral STN DBS even though the pathological mechanism of this increase may need further evaluation.

## Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jocn.2014.07.016.

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